REMARKS

Claims 1-7, 14-32, 50 and 52-72 were pending in the subject application. Of these, claim 61 was allowed and claims 69-72 were indicated as allowable. Applicants have hereinabove canceled claims 55-57, amended claims 1, 3, 5, 14-16, 23-32, 50, 52-54, 58 and 61-64, and added new claims 73-91. Accordingly, claims 1-7, 14-32, 50, 52-54 and 58-91 are currently pending in the subject application.

Support for the amendment to claim 15 may be found, *inter alia*, on page 25, line 8, and on page 43, line 17 of the subject application.

Support for the amendment to claim 64 may be found, *inter alia*, on page 25, line 5, and on page 27, line 10 of the subject application.

Courtesy Copy of Information Disclosure Statement

In Section 3 of the August 30, 2002 Office Action, the Examiner acknowledged receipt of the form PTO-1449 and of the post card receipt supplied by the applicants. However, the Examiner indicated that none of the references have been found.

To ensure that the Patent Office files are complete, applicants are filing this Amendment by Express Mail and attaching a courtesy copy of the Information Disclosure Statement filed June 29, 2001, including all of the 87 references. Applicants look forward to receiving the form PTO-1449 initialed by the Examiner upon consideration of the cited references.

Objections to Claims

In Section 4, the Examiner objected to claims 2-4 alleging they are substantial duplicates of claim 1, and also objected to claims 6 and 7 alleging they are substantial duplicates of claim 5. The Examiner stated that a distinction is not seen between the limitations "substantially free of the A polymorph" [in claim 3] and "substantially homogeneous" [in claim 1], and alleged that the claims are drawn to the same substance with the same purity limitation.

Initially, applicants point out that claim 1 has been amended to recite "A homogeneous crystalline polymorph ... B," claim 3 has been amended to recite the "B polymorph ... which is free of the A polymorph," and claim 5 has been amended to recite a composition which "is free of the A polymorph."

In response to the objection, applicants respectfully point out that being "free of the A polymorph" is not synonymous with being "homogeneous". For example, a composition of matter that is free of A, may not necessarily be substantially free of X. A homogenous composition of matter would be the same material at every point throughout the composition of matter. Therefore, the terms are not synonymous, and applicants respectfully request that the Examiner reconsider these terms and withdraw the objection.

Regarding the similar objection to claims 2, 4, 6 and 7, applicants submit that these claims are proper dependent claims because each further limits the claim from which it depends by reciting additional data points. Each of claims 1, 3 and 5 recites ten (10) data points. Claim 6 recites 45 data points, i.e. an additional 35 data points more than its

respective claim from which it depends. Claim 2, 4 and 7 each recites a continuum of data points, i.e. the full diffraction pattern in graph form, adding a continuum of data points to its respective claim from which it depends. Because claim 2, 4, 6 and 7 each further limits the claim from which it depends, each of these claims is a proper dependent claim.

The sections cited by the Examiner, namely 37 C.F.R. § 1.75 and M.P.E.P. § 706.03(k) do not prohibit applicants from defining their invention by using any and all of, a continuum of data point, 45 data point or 10 data point. In fact, M.P.E.P. § 706.03(k) specifically states that, "court decisions have confirmed applicant's right to restate (i.e., by plural claiming) the invention in a reasonable number of ways. Indeed, a *mere difference in scope between claims* has been held to be enough." (Emphasis added). Each of claims 2-4, 6 and 7 certainly recites a different scope. Accordingly, the objections to claims 2-4, 6 and 7 are improper and should be withdrawn.

Claims 55-57 have been canceled without prejudice. Accordingly, the objection to claims 56 and 57 under 37 C.F.R. 1.75 as being a substantial duplicate of claim 55, is moot.

In Section 7 of the August 30, 2002 Office Action, the Examiner objected to claim 58 under 37 C.F.R. 1.75 as allegedly a substantial duplicate of claim 5. The Examiner stated that it is not logical that a composition intended for therapy, as is claim 5, would not contain a therapeutically effective amount of the compound of claim 1.

In response, applicants respectfully note that while claim 58

is directed to a pharmaceutical composition, claim 5 is broader to cover, for example, bulk form compositions in transit. Therefore, claim 58 is not a substantial duplicate of claim 5, and the objection to claim 58 should be withdrawn.

In Section 8 of the August 30, 2002 Office Action, the Examiner objected to claim 62 under 37 C.F.R. 1.75 as allegedly a substantial duplicate of claim 5. The Examiner stated that applicants have chosen a different and ultimately equivalent way of expressing the X-ray data, and that both are compositions of the identical substance.

In response, applicants respectfully direct the Examiner to their remarks above because similar remarks are appropriate for claim 62. Applicants have amended claim 62 to recite "homogeneous," while claim 5 recites "free of the A polymorph." Consequently, the objection to claim 62 should be withdrawn.

Rejection under 35 U.S.C. § 112, first paragraph - claims 14 and 17-22

In Section 9 of the August 30, 2002 Office Action, the Examiner rejected claims 14 and 17-22 under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably enable one skilled in the relevant art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The Examiner alleged that applicants are not enabled for treatment of "abnormal cell growth" generally. The Examiner cited *In re Buting* 163 USPQ 689, for the preposition that evidence involving a single compound and two types of cancer was not found sufficient to

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establish the enablement of claims directed to a method of treating seven types of cancer with members of *a class of several compounds*. The Examiner noted applicants' argument that claim 14 is drawn to the treatment of specific cancers, and noted the clinical data presented on the pages spanning 50-53. However, the Examiner alleged that applicants' argument is not persuasive because claim 14 is not limited to specific cancers.

In response, applicants have amended claim 14 to recite abnormal cell growth of a cell expressing the epidermal growth factor receptor (EGFR). As noted by the Examiner, Phase I and II Clinical Studies are described on pages 50 to 53 of the subject specification for non-small cell lung cancer, head and neck cancer, refractory ovarian cancer, colorectal cancer, renal carcinoma. All of the cancers of the clinical trials are EGFR positive tumor types. Furthermore, as noted in the description of the clinical trials on page 52, lines 32-35, other EGFR positive tumor types have been documented to be affected by the specific compound. Also, on page 1 of their specification, applicants disclose that the specific compound is known to be an inhibitor of the epidermal growth factor receptor (EGFR), and is therefore useful for the treatment of associated diseases. The diseases which fall within this class are described, for example, on pages 24-29 of the subject specification. Therefore, applicants have enabled the treatment of any disease by the inhibition of the epidermal growth factor receptor (EGFR).

Accordingly, applicants respectfully request that the Examiner reconsider and withdraw the rejection of claim 14 and 17-22, as amended, under 35 U.S.C. § 112, first paragraph.

Rejection under 35 U.S.C. 112, first paragraph - claim 50

In Section 10 of the August 30, 2002 Office Action, the Examiner rejected claim 50 under 35 U.S.C. 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The Examiner alleged that applicants are not enabled for preventing basal or squamous cell carcinoma. The Examiner also alleged that the only established prophylactics are vaccines not the N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine salt such as present here. The Examiner alleged that despite intensive efforts, pharmaceutical science has been unable to find a way of getting a compound to be effective for the prevention of proliferative diseases generally. The Examiner stated that under such circumstances, it is proper for the PTO to require evidence that such an unprecedented feat has actually been accomplished, *In re Ferens*, 163 USPQ 609, and no such evidence has been presented in this case. The Examiner further alleged that the failure of skilled scientists to achieve a goal is substantial evidence that achieving such a goal is beyond the skill of practitioners in that art, citing *Genentech vs Novo Nordisk*, 42 USPQ 2nd 1001, 1006.

In response, applicants have amended claim 50 to clarify that administering the recited compound inhibits the *development of* basal or squamous cell carcinoma of the skin. Carcinoma develops after the first cancerous cell is formed. Inhibiting the proliferation of this first cancerous cell will inhibit *development of* the carcinoma. The recited compound is

reasonably expected to inhibit proliferation of a cancerous basal or squamous cell because such cell is EGFR positive. Thus, it is reasonable to expect the recited compound to inhibit proliferation of such first cancerous cell, and, hence, to inhibit the *development of* basal or squamous cell carcinoma of the skin.

Accordingly, applicants respectfully request that the Examiner reconsider and withdraw the rejection of claim 50, as amended, under 35 U.S.C. § 112, first paragraph.

Rejection of claim 63 under 35 U.S.C. § 112, first and second paragraphs

In Section 11 of the August 30, 2002 Final Office Action the Examiner rejected claims 63 under 35 U.S.C. 112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner inquired whether this claim is restricted to cancer therapy or whether there are additional reasons for "inducing differentiation of tumor cells".

In Section 12 of the August 30, 2002 Office Action, the Examiner rejected claim 63 under 35 U.S.C. 112, first paragraph, while being enabling for treating specific tumors, allegedly does not reasonably provide enablement for cancer treatment generally of for other uses of tumor cell differentiation which are not therapeutic.

In response, applicants have amended claim 63 to recite treating a subject with a tumor by inducing differentiation of tumor cells expressing an epidermal growth factor receptor

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(EGFR) in the tumor. Amended claim 63 recites treatment of a specific type of tumors, which the Examiner indicated to be enabled. Accordingly, applicants respectfully request that the Examiner reconsider and withdraw the rejections under 35 U.S.C. § 112, first and second paragraphs, of claim 63, as amended.

Rejection under 35 U.S.C. 102(e) - claims 1-7, 14-23 and 52-54

In Section 13 of the August 30, 2002 Office Action, the Examiner rejected claims 1-7, 14-23, and 52-54 under 35 U.S.C. 102(e) as allegedly anticipated by U.S. Patent No. 5,747,498 to Schnur et al. ("the '498 patent"). The Examiner alleged that the reference teaches the synthesis and crystallization of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine, monohydrochloride in Example 20, lines 30-49, column 22. The Examiner acknowledged that applicants have amply characterized their claimed material, polymorph B, but alleged that there is no side-by-side comparison to the material taught by the reference. The Examiner noted that applicants state in lines 15-19, page 16 [that] the material made by the '498 patent is a mixture of polymorph A and polymorph B, but that there is no data provided in the specification as to the ratio A and B in the prior art. The Examiner questioned could the material prepared by the '498 patent contain substantial amounts of polymorph B, e.g. as high as 70%, or might it be 90%. The Examiner noted that on line 2, page 5 applicants disclose "substantially homogeneous" polymorph B, but questioned what that means, i.e. whether it is 99.9% polymorph B, 90%, or 51%.

The Examiner also noted that the treatment of lung, ovarian, head, neck, colorectal, and renal cancer is taught in lines 8-

11, column 14 of the '498 patent.

In response, applicants have clarified their claims to recite either "homogenous" B, or B "free of A". The amended claims clarify that applicants' claimed subject matter is distinct from mixtures that have detectable amounts of the A polymorph using x-ray diffraction. Accordingly, applicants respectfully request that the Examiner reconsider and withdraw the rejection under 35 U.S.C. 102(e) of claims 1-7, 14-23, and 52-54, as amended.

Rejection under 35 U.S.C. 102(e) - claims 55-60

In Section 14 of the August 30, 2002 Office Action, the Examiner rejected claims 55-60 under 35 U.S.C. 102(e) as allegedly anticipated by the '498 patent. The Examiner alleged that compositions are taught in the '498 patent in the passage spanning line 63, column 15 to line 45, column 16, and tablets are specifically mentioned in line 64. The Examiner also alleged that the silence of the reference as to the amount of polymorph B present does not make applicants' claims patentable for the reasons cited above.

In response, applicants have canceled claims 55-57 and amended claims 58-60 to clarify that the composition is "free of the A polymorph." As amended, applicants' claims 58-60 clearly distinguish over mixtures as discussed above. Accordingly, applicants respectfully request that the Examiner reconsider and withdraw the rejection under 35 U.S.C. 102(e) of claims 58-60, as amended.

Rejection under 35 U.S.C. 102(e) - claims 62-68

In Section 15 of the August 30, 2002 Office Action, the Examiner rejected claims 62-68 under 35 U.S.C. 102(e) as allegedly anticipated by the '498 patent. The Examiner alleged that the prior art and applicants' silence as to the ratios do not make their claims patentable for reasons cited above. The Examiner also noted that cancer therapy broadly is found in claim 28 of the '498 patent. The Examiner also noted that applicants' claim 64 is an independent claim with no limitation as to crystal form, and that treatment of lung cancer, leukemia, and cervical tumors is taught in lines 6-16, column 14 of the '498 patent; that treatment of "immunological disorders" is taught in 28, column 14 fo the '498 patent; and treatment of skin cancer is taught in claim 29 of the '498 patent. The Examiner also noted that the concept of additional anti-tumor agents is taught in lines 46-51, column 16 of the '498 patent.

In response, applicants have amended claims 62 to recite that the composition comprises "homogeneous" B polymorph, and amended claim 63 to depend on amended claims 3 and 5 which recite the B polymorph "free of the A polymorph". As amended, applicants' claims 62 and 63 clearly distinguish over mixtures, as discussed above.

Applicants have also amended claims 64-68 to recite conditions which are not disclosed in the '498 patent. Although lung cancer is mentioned in the '498 patent, NSCLC is not.

Accordingly, applicants respectfully request that the Examiner reconsider and withdraw the rejection under 35 U.S.C. 102(e) of claims 62-68, as amended.

Rejection under 35 U.S.C. 103(a)

In Section 16 of the August 30, 2002 Office Action, the Examiner rejected claims 24-32 under 35 U.S.C. § 103(a) as allegedly unpatentable over the '498 patent. The Examiner alleged that the '498 patent teaches crystallization of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine, monohydrochloride from chloroform and ether, while applicants claim crystallization from water and alcohol. The Examiner alleged that the difference between the claimed and taught processes is the solvent employed, and changes in solvent are a matter of routine experimentation to the process chemist trying safer and less flammable solvents for the pilot plant. The Examiner quoted the Board of Patent Appeals and Interferences in *Ex parte Goldschmidt*, 123 USPQ 41 "It is our opinion that is does not amount to invention for the skilled chemist...to determine...which specific organic solvent is most suitable". The Examiner, however, did point out that if applicants establish novelty of their crystal form, then their process would be non-obvious, citing *In re Ochiai*, 37 USPQ2d 1127.

In response, applicants contend that the novelty of their claimed crystal form has been established as discussed above. Accordingly, the rejection under 35 U.S.C. § 103 of process claims 24-32 should be withdrawn.

Allowable Subject Matter

In Sections 17 and 18 of the August 30, 2002 Office Action, the Examiner indicated that claim 61 is allowed, and claims 69-72 would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Applicants have amended claim 64 from which claims 69-71 depend. Applicants contend that claim 64, as amended, should be allowed for the reasons set forth above. Therefore, claims 69-72 should be allowed because they now depend on an allowed base claim.

In addition, applicants have also added new claim 74, which should be allowed because it recites all of the limitation of allowable claims 69-72.

Conclusion

In view of the amendments and remarks hereinabove, applicants respectfully request that the Examiner reconsider and withdraw the rejections and objection set forth in the August 30, 2002 Office Action and earnestly solicit allowance of the claims, as amended.

No fee, other than the $930.00 for a three-month extension of time, is deemed necessary in connection with the filing of this Amendment. However, if any additional fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,

Gary J. Gershik

John P. White
Registration No. 28,678
Gary J. Gershik
Registration No. 39,992
Attorneys for Applicants
Cooper & Dunham LLP
1185 Avenue of the Americas
New York, New York 10036
(212) 278-0400

Attachment A

(Claims with marking to show changes)

1. (Amended) A ~~substantially~~ homogeneous crystalline polymorph of the hydrochloride salt of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine designated the B polymorph that exhibits an X-ray powder diffraction pattern having characteristic peaks expressed in degrees 2-theta at approximately 6.26, 12.48, 13.39, 16.96, 20.20, 21.10, 22.98, 24.46, 25.14, and 26.91.

2. The polymorph of claim 1, characterized by the X-ray powder diffraction pattern shown in Figure 3.

3. (Amended) A crystalline polymorph of the hydrochloride salt of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine designated the B polymorph that exhibits an X-ray powder diffraction pattern having characteristic peaks expressed in degrees 2-theta at approximately 6.26, 12.48, 13.39, 16.96, 20.20, 21.10, 22.98, 24.46, 25.14 and, 26.91, which is ~~substantially~~ free of the A polymorph.

4. The polymorph of claim 3, characterized by the X-ray powder diffraction pattern shown in Figure 3.

5. (Amended) A composition comprising a ~~substantially homogeneous~~ crystalline polymorph of the hydrochloride salt of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine designated the B polymorph that exhibits an X-ray powder diffraction pattern having characteristic peaks expressed in degrees 2-theta at approximately 6.26, 12.48, 13.39, 16.96, 20.20, 21.10, 22.98, 24.46, 25.14 and, 26.91, and a carrier, wherein the composition is free of the A polymorph.

6. The composition of claim 5, wherein the hydrochloride salt of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine exhibits an X-ray powder diffraction pattern having characteristic peaks expressed in degrees 2-theta at approximately:

2-Theta	I(rel)	2-Theta	I(rel)	2-Theta	I(rel)	2-Theta	I(rel)	2-Theta	I(rel)
6.255	100.0	17.668	2.5	22.982	4.8	27.534	0.9	32.652	1.7
7.860	3.2	18.193	0.7	23.589	2.3	28.148	1.5	33.245	1.7
9.553	3.9	18.749	1.5	23.906	3.0	28.617	4.3	34.719	1.5
11.414	1.5	19.379	1.0	24.459	6.8	29.000	1.4	35.737	0.8

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12.483	6.4	20.196	14.4	25.138	10.0	29.797	2.1	36.288	1.0
13.385	9.6	20.734	4.2	25.617	3.7	30.267	0.9	36.809	0.6
14.781	2.1	21.103	14.4	25.908	3.9	30.900	1.6	37.269	1.1
15.720	2.9	21.873	4.7	26.527	2.8	31.475	2.2	37.643	1.4
16.959	5.5	22.452	4.5	26.911	5.6	31.815	2.4	38.114	1.7

7. The composition of claim 5, wherein the N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine hydrochloride in the polymorph B form is characterized by the X-ray powder diffraction pattern shown in Figure 3.

14. (Twice Amended) A method of treating abnormal cell growth of a cell expressing the epidermal growth factor receptor (EGFR) in a mammal which comprises administering to said mammal a therapeutically effective amount of the polymorph of claim ~~1~~ 3.

15. (Amended) The method of claim 14, wherein the ~~method is for the treatment of a cancer selected from~~ abnormal cell growth is brain, squamous cell, bladder, gastric, pancreatic, hepatic, glioblastoma multiforme breast, head, neck, esophageal, prostate, colorectal, lung, renal, kidney, ovarian, gynecological ~~and~~ or thyroid cancer.

16. (Amended) The method of claim 14, wherein the ~~method of for the treatment of a cancer selected from~~ abnormal cell growth is non-small cell lung cancer (NSCLC), refractory ovarian cancer, or head and neck cancer~~, colorectal cancer and renal cancer~~.

17. The method of claim 14, wherein the therapeutically effective amount is from about 0.001 to about 100 mg/kg/day.

18. The method of claim 14, wherein the therapeutically effective amount is from about 1 to about 35 mg/kg/day.

19. The method of claim 14, wherein the therapeutically effective amount is from about 1 to about 7000 mg/day.

20. The method of claim 19, wherein the therapeutically effective amount is from about 5 to about 2500 mg/day.

21. The method of claim 20, wherein the therapeutically effective amount is from about 5 to about 200 mg/day.

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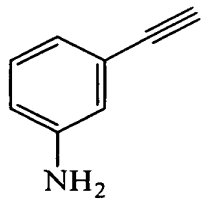
22. The method of claim 21, wherein the therapeutically effective amount is from about 25 to about 200 mg/day.

23. (Twice Amended) A method for the treatment of abnormal cell growth <u>of a cell expressing the epidermal growth factor receptor (EGFR)</u> in a mammal which comprises administering to said mammal a therapeutically effective amount of the polymorph of claim ~~1~~ <u>3</u> in combination with an anti-tumor agent selected from the group consisting of a mitotic inhibitor, an alkylating agent, an anti-metabolite, an intercalating antibiotic, a growth factor inhibitor, a cell cycle inhibitor, an enzyme, a topoisomerase inhibitor, a biological response modifier, an anti-hormone, and an anti-androgen.

24. (Amended) A ~~method of~~ <u>process for</u> preparing a crystalline polymorph of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine hydrochloride designated the B polymorph<u>, which is free of the A polymorph,</u> which comprises the step of recrystallizing N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine hydrochloride in a solvent comprising alcohol.

25. (Amended) The ~~method~~ <u>process</u> of claim 24, wherein the solvent further comprises water.

26. (Amended) The ~~method~~ <u>process</u> of claim 24, wherein N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine hydrochloride is prepared by coupling a compound of formula 6



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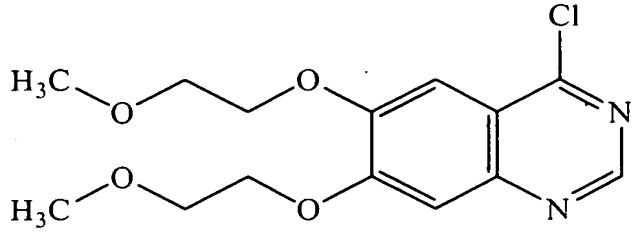
with a compound of formula 4



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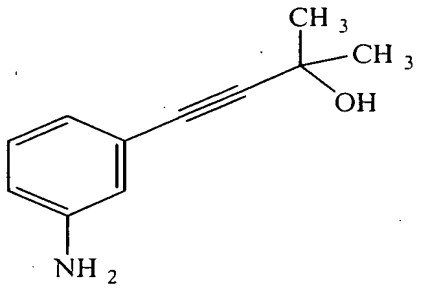
27. (Amended) The ~~method~~ process of claim 26, wherein said compound of formula 6 is prepared by ~~reacting~~ heating a compound of formula 5



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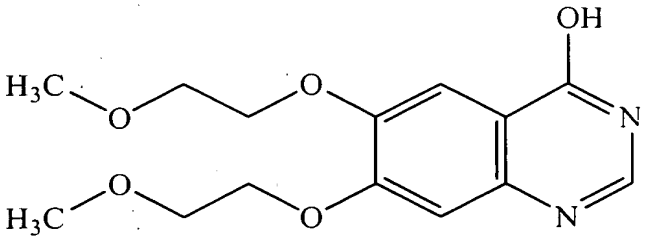
in a suspension of metal alkali and solvent ~~and with heating~~.

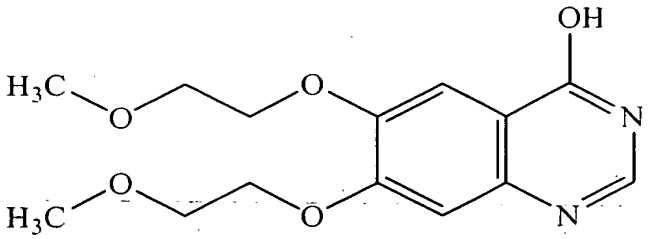
28. (Amended) The ~~method~~ process of claim 26, wherein said compound of formula 4 is prepared by chlorinating a compound of formula 3



3.

29. (Amended) A ~~method~~ process for the production of the polymorph B of claim 1 comprising the steps of:

a) substitution chlorination of starting quinazolinamine compound of formula 3



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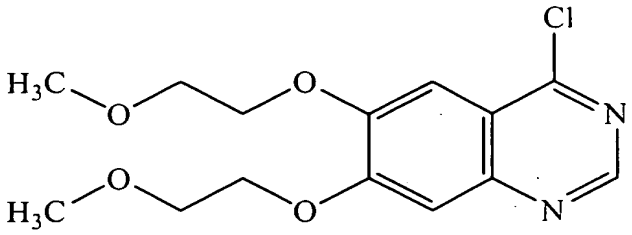
having an hydroxyl group, to provide a compound of formula 4



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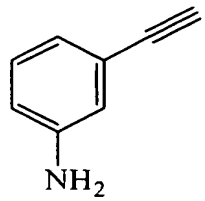
by reaction thereof in a solvent mixture of thionyl chloride, methylene chloride and dimethylformamide,

b) preparation of a compound of formula 6



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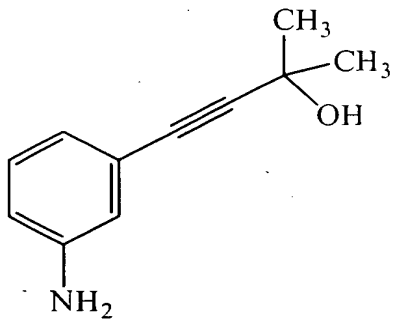
in situ from starting material of compound of formula 5



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by ~~reaction of the latter~~ heating the compound of formula 5 in a suspension of metal alkali and solvent ~~and with heating~~;

c) reaction of the compound of formula 6 in situ with the compound of formula 4 wherein the compound of formula 6 replaces the chlorine in the compound of formula 4 to give the N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine hydrochloride;

d) recrystallizing the N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine hydrochloride, in alcohol, into the polymorph B form.

30. (Amended) The ~~method~~ process of claim 29, wherein the substitution chlorination is quenched in the presence of aqueous sodium hydroxide.

31. (Amended) The ~~method~~ process of claim 29, wherein the substitution chlorination is quenched in the presence of aqueous sodium bicarbonate.

32. (Amended) The ~~method~~ process of claim 29, wherein the substitution chlorination is quenched in the presence of aqueous potassium hydroxide, aqueous potassium bicarbonate, aqueous potassium carbonate, aqueous sodium carbonate, or a mixture thereof.

50. (Twice Amended) A method ~~for prophylaxis against~~ of inhibiting the development of basal or squamous cell carcinoma of the skin in areas exposed to the sun or in persons of high risk to said carcinoma, said method comprising administering to said persons a therapeutically effective amount of a pharmaceutical composition comprised of at least one of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-

quinazolinamine, and pharmaceutically acceptable salts thereof in anhydrous and hydrate forms, so as to thereby ~~result in prophylaxis against~~ inhibit the development of basal or squamous cell carcinoma of the skin.

52. (Amended) A ~~method~~ process of making a composition which composition comprises ~~substantially homogeneous~~ a crystalline polymorph of the hydrochloride salt of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine designated the B polymorph that exhibits an X-ray powder diffraction pattern having characteristic peaks expressed in degrees 2-theta at approximately 6.26, 12.48, 13.39, 16.96, 20.20, 21.10, 22.98, 24.46, 25.14 and, 26.91, which is free of the A polymorph, comprising admixing the crystalline polymorph ~~of claim 1~~ with a carrier.

53. (Amended) The ~~method~~ process of claim 52, wherein the N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine hydrochloride in the polymorph B form is characterized by the X-ray powder diffraction pattern shown in Figure 3.

54. (Amended) The ~~method~~ process of claim 52, wherein the carrier is a pharmaceutically acceptable carrier.

~~55. A composition comprising a crystalline polymorph of the hydrochloride salt of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine designated the B polymorph that exhibits an X-ray powder diffraction pattern having characteristic peaks expressed in degrees 2-theta at approximately 6.26, 12.48, 13.39, 16.96, 20.20, 21.10, 22.98, 24.46, 25.14 and, 26.91 in a weight % of the B polymorph relative to the A polymorph which is at least 70%.~~

~~56. The composition of claim 55, wherein the B polymorph of the hydrochloride salt of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine exhibits an X-ray powder diffraction pattern having characteristic peaks expressed in degrees 2-theta at approximately:~~

~~2-Theta~~	~~I(rel)~~	~~2-Theta~~	~~I(rel)~~	~~2-Theta~~	~~I(rel)~~	~~2-Theta~~	~~I(rel)~~	~~2-Theta~~	~~I(rel)~~
~~6.255~~	~~100.0~~	~~17.668~~	~~2.5~~	~~22.982~~	~~4.8~~	~~27.534~~	~~0.9~~	~~32.652~~	~~1.7~~
~~7.860~~	~~3.2~~	~~18.193~~	~~0.7~~	~~23.589~~	~~2.3~~	~~28.148~~	~~1.5~~	~~33.245~~	~~1.7~~
~~9.553~~	~~3.9~~	~~18.749~~	~~1.5~~	~~23.906~~	~~3.0~~	~~28.617~~	~~4.3~~	~~34.719~~	~~1.5~~
~~11.414~~	~~1.5~~	~~19.379~~	~~1.0~~	~~24.459~~	~~6.8~~	~~29.000~~	~~1.4~~	~~35.737~~	~~0.8~~
~~12.483~~	~~6.4~~	~~20.196~~	~~14.4~~	~~25.138~~	~~10.0~~	~~29.797~~	~~2.1~~	~~36.288~~	~~1.0~~
~~13.385~~	~~9.6~~	~~20.734~~	~~4.2~~	~~25.617~~	~~3.7~~	~~30.267~~	~~0.9~~	~~36.809~~	~~0.6~~
~~14.781~~	~~2.1~~	~~21.103~~	~~14.4~~	~~25.908~~	~~3.9~~	~~30.900~~	~~1.6~~	~~37.269~~	~~1.1~~
~~15.720~~	~~2.9~~	~~21.873~~	~~4.7~~	~~26.527~~	~~2.8~~	~~31.475~~	~~2.2~~	~~37.643~~	~~1.4~~
~~16.959~~	~~5.5~~	~~22.452~~	~~4.5~~	~~26.911~~	~~5.6~~	~~31.815~~	~~2.4~~	~~38.114~~	~~1.7~~

~~57. The composition of claim 55, wherein the N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine hydrochloride in the polymorph B form is characterized by the X-ray powder diffraction pattern shown in Figure 3.~~

58. (Amended) A pharmaceutical composition which comprises a therapeutically effective amount of the polymorph of claim ~~1~~ 3 and a pharmaceutically acceptable carrier, wherein the pharmaceutical composition is free of the A polymorph.

59. The pharmaceutical composition of claim 58, wherein said composition is adapted for oral administration.

60. The pharmaceutical composition of claim 59, wherein the pharmaceutical composition is in the form of a tablet.

61. (Amended) A ~~method~~ process for the production of a crystalline polymorph of the hydrochloride salt of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine designated the B polymorph by recrystallization comprising the steps of:

e) heating to reflux alcohol, water and the hydrochloride salt of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine so as to form a solution;
f) cooling the solution to between about 65 and 70 °C;
g) clarifying the solution; and

h) precipitating polymorph B by further cooling the clarified solution.

62. (Amended) A composition consisting of a ~~comprising a substantially~~ homogeneous crystalline polymorph of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine hydrochloride in the form of polymorph B, which is characterized by the following peaks:

Polymorph B

Anode: Cu - Wavelength 1 1.54056 Wavelength 2: 1.54439 (Rel Intensity:0.500)
Range # 1 - Coupled 3.000 to. 40.040 StepSize: 0.040 StepTime 1.00
Smoothing Width: 0.300 Threshold: 1.0

d(A)	I(rel)	d(A)	I(rel)	d(A)	I(rel)	d(A)	I(rel)	d(A)	I(rel)
14.11826	100.0	5.01567	2.5	3.86656	4.8	3.23688	0.9	2.74020	1.7
11.23947	3.2	4.87215	0.7	3.76849	2.3	3.16755	1.5	2.69265	1.7
9.25019	3.9	4.72882	1.5	3.71927	3.0	3.11673	4.3	2.58169	1.5
7.74623	1.5	4.57666	1.0	3.63632	6.8	3.07644	1.4	2.51043	0.8
7.08519	6.4	4.39330	14.4	3.53967	10.0	2.99596	2.1	2.47356	1.0
6.60941	9.6	4.28038	4.2	3.47448	3.7	2.95049	0.9	2.43974	0.6
5.98828	2.1	4.20645	14.4	3.43610	3.9	2.89151	1.6	2.41068	1.1
5.63253	2.9	4.06007	4.7	3.35732	2.8	2.83992	2.2	2.38755	1.4
5.22369	5.5	3.95667	4.5	3.31029	5.6	2.81037	2.4	2.35914	1.7

or,

Polymorph B

Anode: Cu - Wavelength 1 1.54056 Wavelength 2: 1.54439 (Rel Intensity:0.500)
Range# 1 - Coupled: 3.000 to 40.040 StepSize 0.040 StepTime: 1.00
Soothing Width:0.300 Threshold: 1.0

2-Theta	I(rel)	2-Theta	I(rel)	2-Theta	I(rel)	2-Theta	I(rel)	2-Theta	I(rel)
6.255	100.0	17.668	2.5	22.982	4.8	27.534	0.9	32.652	1.7
7.860	3.2	18.193	0.7	23.589	2.3	28.148	1.5	33.245	1.7
9.553	3.9	18.749	1.5	23.906	3.0	28.617	4.3	34.719	1.5
11.414	1.5	19.379	1.0	24.459	6.8	29.000	1.4	35.737	0.8
12.483	6.4	20.196	14.4	25.138	10.0	29.797	2.1	36.288	1.0
13.385	9.6	20.734	4.2	25.617	3.7	30.267	0.9	36.809	0.6
14.781	2.1	21.103	14.4	25.908	3.9	30.900	1.6	37.269	1.1
15.720	2.9	21.873	4.7	26.527	2.8	31.475	2.2	37.643	1.4
16.959	5.5	22.452	4.5	26.911	5.6	31.815	2.4	38.114	1.7

and at least one carrier.

63. (Amended) A method of treating a subject with a tumor by inducing differentiation of tumor cells expressing an epidermal growth factor receptor (EGFR) in ~~a~~ the tumor comprising contacting the cells with an effective amount of the compound of claim ~~1~~ 3, or a composition of claims ~~3 or 6~~ 5 so as to thereby ~~differentiate the tumor cells~~ treat the subject.

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64. (Amended) A method for the treatment of NSCLC (non small cell lung cancer), pediatric malignancies, cervical and other tumors caused or promoted by human papilloma virus (HPV), endometrial cancer, glioma, melanoma, Barrett's esophagus (pre-malignant syndrome), adrenal ~~and skin~~ cancers ~~and auto immune~~, neoplastic cutaneous diseases ~~and~~ or atherosclerosis in a mammal comprising administering to said mammal a therapeutically effective amount of a pharmaceutical composition comprised of at least one of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine, and pharmaceutically acceptable salts thereof in anhydrous and hydrate forms.

65. The method of claim 64, wherein the treatment further comprises a palliative or neo-adjuvant/adjuvant monotherapy.

66. The method of claim 64, wherein the treatment further comprises blocking epidermal growth factor receptors (EGFR).

67. The method of claim 64, for use in treatment of tumors that express EGFRvIII.

68. The method of claim 64, wherein the treatment further comprises a combination with any of chemotherapy and immunotherapy.

69. The method of claim 64, wherein the treatment further comprises, treatment with either or both anti-EGFR and anti-EGF antibodies.

70. The method of claim 64, wherein the treatment further comprises a further administration to said mammal of a member of the group consisting of inhibitors of MMP (matrix-metallo-proteinase), VEGFR (vascular endothelial growth factor receptor), farnesyl transferase, $CTLA_4$ (cytotoxic T-lymphocyte antigen 4) and erbB2, MAb to VEGFr, rhuMAb-VEGF, erbB2 MAb and avb3 Mab.

71. The method of claim 64, wherein the pharmaceutical compounds are used as radiation sensitizers for cancer treatment or in combination with anti-hormonal therapies.

72. The method of claim 64, wherein the pharmaceutical compounds are used for the inhibition of tumor growth in humans in a regimen with radiation treatment.

73. (New) The method of claim 64, wherein the pharmaceutical composition comprises a crystalline polymorph of the hydrochloride salt of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine designated the B polymorph that exhibits an X-ray powder diffraction pattern having characteristic peaks expressed in degrees 2-theta at approximately 6.26, 12.48, 13.39, 16.96, 20.20, 21.10, 22.98, 24.46, 25.14 and, 26.91, and a pharmaceutically acceptable carrier, wherein the composition is free of the A polymorph.

74. (New) A method for the treatment of NSCLC (non small cell lung cancer), pediatric malignancies, cervical and other tumors caused or promoted by human papilloma virus (HPV), endometrial cancer, glioma, melanoma, Barrett's esophagus (pre-malignant syndrome), adrenal and skin cancers, autoimmune, neoplastic cutaneous diseases or atherosclerosis in a mammal comprising administering to said mammal a therapeutically effective amount of a pharmaceutical composition comprised of at least one of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine, and pharmaceutically acceptable salts thereof in anhydrous and hydrate forms,
wherein the treatment further comprises,
a) treatment with either or both anti-EGFR and anti-EGF antibodies,
b) administration to said mammal of a member of the group consisting of inhibitors of MMP (matrix-metallo-proteinase), VEGFR (vascular endothelial growth factor receptor), farnesyl transferase, $CTLA_4$ (cytotoxic T-lymphocyte antigen 4) and erbB2, MAb to VEGFr, rhuMAb-VEGF, erbB2 MAb and avb3 Mab, or
c) radiation treatment.

75. (New) The method of claim 15, wherein the abnormal cell growth is pancreatic cancer.

76. (New) The method of claim 15, wherein the abnormal cell growth is colorectal cancer.

77. (New) The method of claim 15, wherein the abnormal cell growth is prostate cancer.

78. (New) The method of claim 15, wherein the abnormal cell growth is breast cancer.

79. (New) The method of claim 15, wherein the abnormal cell growth is esophageal cancer.

80. (New) The method of claim 15, wherein the abnormal cell growth is ovarian cancer.

81. (New) The method of claim 15, wherein the abnormal cell growth is glioblastoma multiforme.

82. (New) The method of claim 15, wherein the abnormal cell growth is hepatic cancer.

83. (New) The method of claim 15, wherein the abnormal cell growth is renal cancer.

84. (New) The method of claim 15, wherein the abnormal cell growth is gastric cancer.

85. (New) The method of claim 15, wherein the abnormal cell growth is bladder cancer.

86. (New) The method of claim 16, wherein the abnormal cell growth is non-small cell lung cancer (NSCLC).

87. (New) The method of claim 16, wherein the abnormal cell growth is head and neck cancer.

88. (New) The method of claim 64 for the treatment of non-small cell lung cancer (NSCLC).

89. (New) The method of claim 64 for the treatment of endometrial cancer.

90. (New) The method of claim 64 for the treatment of glioma.

91. (New) The method of claim 64 for the treatment of melanoma.

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